Année de publication : 2018

Żylicz Jan Jakub, Bousard Aurélie, Žumer Kristina, Dossin François, Mohammad Eusra, Teixiera da Rocha Simão, Schwalb Björn, Syx Laurène, Dingli Florent, Loew Damarys, Cramer Patrick, Heard Edith (2018 Dec 21)

The Implication of Early Chromatin Changes in X Chromosome Inactivation

Cell : 176 : 1-16 : DOI : 10.1016/j.cell.2018.11.041

Résumé

During development, the precise relationships between transcription and chromatin modifications often remain unclear. We use the X chromosome inactivation (XCI) paradigm to explore the implication of chromatin changes in gene silencing. Using female mouse embryonic stem cells, we initiate XCI by inducing Xist and then monitor the temporal changes in transcription and chromatin by allele-specific profiling. This reveals histone deacetylation and H2AK119 ubiquitination as the earliest chromatin alterations during XCI. We show that HDAC3 is pre-bound on the X chromosome and that, upon Xist coating, its activity is required for efficient gene silencing. We also reveal that first PRC1-associated H2AK119Ub and then PRC2-associated H3K27me3 accumulate initially at large intergenic domains that can then spread into genes only in the context of histone deacetylation and gene silencing. Our results reveal the hierarchy of chromatin events during the initiation of XCI and identify key roles for chromatin in the early steps of transcriptional silencing.

Dorian Obino, Luc Fetler, Andrea Soza, Odile Malbec, Juan José Saez, Mariana Labarca, Claudia Oyanadel, Felipe Del Valle Batalla, Nicolas Goles, Aleksandra Chikina, Danielle Lankar, Fabián Segovia-Miranda, Camille Garcia, Thibaut Léger, Alfonso Gonzalez, Marion Espéli, Ana-Maria Lennon-Duménil, Maria-Isabel Yuseff (2018 Dec 13)

Galectin-8 Favors the Presentation of Surface-Tethered Antigens by Stabilizing the B Cell Immune Synapse.

Cell reports : 3110-3122.e6 : DOI : S2211-1247(18)31815-1

Résumé

Complete activation of B cells relies on their capacity to extract tethered antigens from immune synapses by either exerting mechanical forces or promoting their proteolytic degradation through lysosome secretion. Whether antigen extraction can also be tuned by local cues originating from the lymphoid microenvironment has not been investigated. We here show that the expression of Galectin-8-a glycan-binding protein found in the extracellular milieu, which regulates interactions between cells and matrix proteins-is increased within lymph nodes under inflammatory conditions where it enhances B cell arrest phases upon antigen recognition in vivo and promotes synapse formation during BCR recognition of immobilized antigens. Galectin-8 triggers a faster recruitment and secretion of lysosomes toward the B cell-antigen contact site, resulting in efficient extraction of immobilized antigens through a proteolytic mechanism. Thus, extracellular cues can

determine how B cells sense and extract tethered antigens and thereby tune B cell responses in vivo.

Elise Bonvin, Enrico Radaelli, Martin Bizet, Flavie Luciani, Emilie Calonne, Pascale Putmans, David Nittner, Nitesh Kumar Singh, Sara Francesca Santagostino, Valérie Petit, Lionel Larue, Jean Christophe Marine, François Fuks (2018 Dec 13)

TET2-Dependent Hydroxymethylome Plasticity Reduces Melanoma Initiation and Progression.

Cancer research : 482-494 : DOI : 10.1158/0008-5472.CAN-18-1214

Résumé

: Although numerous epigenetic aberrancies accumulate in melanoma, their contribution to initiation and progression remain unclear. The epigenetic mark 5-hydroxymethylcytosine (5hmC), generated through TET-mediated DNA modification, is now referred to as the sixth base of DNA and has recently been reported as a potential biomarker for multiple types of cancer. Loss of 5hmC is an epigenetic hallmark of melanoma, but whether a decrease in 5hmc levels contributes directly to pathogenesis or whether it merely results from disease progression-associated epigenetic remodeling remains to be established. Here, we show that NRAS-driven melanomagenesis in mice is accompanied by an overall decrease in 5hmC and specific 5hmC gains in selected gene bodies. Strikingly, genetic ablation of in mice cooperated with oncogenic NRAS to promote melanoma initiation while suppressing specific gains in 5hmC. We conclude that TET2 acts as a barrier to melanoma initiation and progression, partly by promoting 5hmC gains in specific gene bodies. SIGNIFICANCE: This work emphasizes the importance of epigenome plasticity in cancer development and highlights the involvement of druggable epigenetic factors in cancer.

Eleonora Meschi, Pierre Léopold*, Renald Delanoue, (*Corr. author) (2018 Dec 10)

An EGF-Responsive Neural Circuit Couples Insulin Secretion with Nutrition in Drosophila.

Developmental cell : DOI : 10.1016/j.devcel.2018.11.029

Résumé

Developing organisms use fine-tuning mechanisms to adjust body growth to ever-changing nutritional conditions. In Drosophila, the secretory activity of insulin-producing cells (IPCs) is central to couple systemic growth with amino acids availability. Here, we identify a subpopulation of inhibitory neurons contacting the IPCs (IPC-connecting neurons or ICNs) that play a key role in this coupling. We show that ICNs respond to growth-blocking peptides (GBPs), a family of fat-body-derived signals produced upon availability of dietary amino acids. We demonstrate that GBPs are atypical ligands for the fly EGF receptor (EGFR). Upon activation of EGFR by adipose GBPs, ICN-mediated inhibition of IPC function is relieved, allowing insulin secretion. Our study reveals an unexpected role for EGF-like metabolic hormones and EGFR signaling as critical modulators of neural activity, coupling insulin

secretion to the nutritional status.

Marion Salou, François Legoux, Jules Gilet, Aurélie Darbois, Anastasia du Halgouet, Ruby Alonso, Wilfrid Richer, Anne-Gaëlle Goubet, Céline Daviaud, Laurie Menger, Emanuele Procopio, Virginie Premel, Olivier Lantz (2018 Dec 7)

A common transcriptomic program acquired in the thymus defines tissue residency of MAIT and NKT subsets.

The Journal of experimental medicine : 133-151 : DOI : 10.1084/jem.20181483

Résumé

Mucosal-associated invariant T (MAIT) cells are abundant T cells with unique specificity for microbial metabolites. MAIT conservation along evolution indicates important functions, but their low frequency in mice has hampered their detailed characterization. Here, we performed the first transcriptomic analysis of murine MAIT cells. MAIT1 (RORγt) and MAIT17 (RORγt) subsets were markedly distinct from mainstream T cells, but quasi-identical to NKT1 and NKT17 subsets. The expression of similar programs was further supported by strong correlations of MAIT and NKT frequencies in various organs. In both mice and humans, MAIT subsets expressed gene signatures associated with tissue residency. Accordingly, parabiosis experiments demonstrated that MAIT and NKT cells are resident in the spleen, liver, and lungs, with LFA1/ICAM1 interactions controlling MAIT1 and NKT1 retention in spleen and liver. The transcriptional program associated with tissue residency was already expressed in thymus, as confirmed by adoptive transfer experiments. Altogether, shared thymic differentiation processes generate « preset » NKT and MAIT subsets with defined effector functions, associated with specific positioning into tissues.

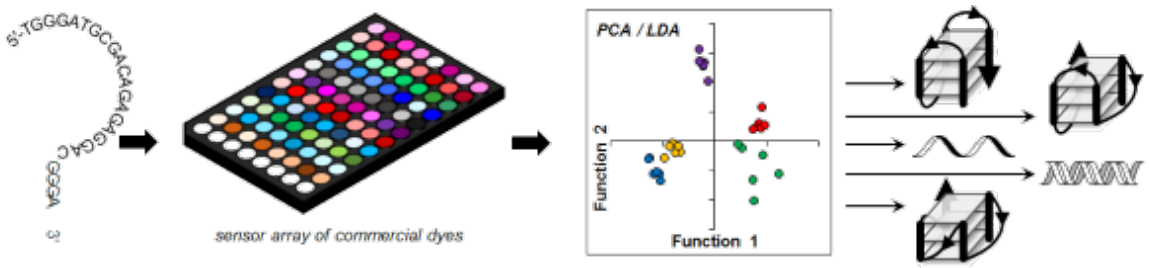
Année de publication : 2019

Michela Zuffo, Xiao Xie, Anton Granzhan (2018 Dec 6)

Strength in Numbers: Development of a Fluorescence Sensor Array for Secondary Structures of DNA.

Chemistry - A European Journal : 25 : 1812–1818 : DOI : 10.1002/chem.201805422

Résumé



High-throughput assessment of secondary structures adopted by DNA oligonucleotides is

currently hampered by the lack of suitable biophysical methods. Fluorescent sensors hold great potential in this respect; however, the moderate selectivity that they display for one DNA conformation over the others constitutes a major drawback to the development of accurate assays. Moreover, the use of single sensors impedes a comprehensive classification of the tested sequences. Herein, we propose to overcome these limitations through the development of a fluorescence sensor array constituted by easily accessible, commercial dyes. Multivariate analysis of the emission data matrix produced by the array allows to explore the conformational preferences of DNA sequences of interest, either by calculating the probability of group membership in the six predefined structural categories (three G-quadruplex groups, double-stranded, and two groups of single-stranded forms), or by revealing their particular structural features. The assay enables rapid screening of synthetic DNA oligonucleotides in a 96-wells plate format.

Année de publication : 2018

Alexandra Frazao, Meriem Messaoudene, Nicolas Nunez, Nicolas Dulphy, France Roussin, Christine Sedlik, Laurence Zitvogel, Eliane Piaggio, Antoine Toubert, Anne Caignard (2018 Dec 6)
CD16NKG2A Natural Killer Cells Infiltrate Breast Cancer-Draining Lymph Nodes.
Cancer immunology research : 208-218 : DOI : 10.1158/2326-6066.CIR-18-0085

Résumé

Tumor-draining lymph nodes (TD-LNs) are the first site of metastasis of breast cancer. Natural killer (NK) cells that infiltrate TD-LNs [including noninvaded (NI) or metastatic (M)-LNs from breast cancer patients] and NK cells from healthy donor (HD)-LNs were characterized, and their phenotype analyzed by flow cytometry. Low percentages of tumor cells invaded M-LNs, and these cells expressed ULBP2 and HLA class I molecules. Although NK cells from paired NI and M-LNs were similar, they expressed different markers compared with HD-LN NK cells. Compared with HD-LNs, TD-LN NK cells expressed activating DNAM-1, NKG2C and inhibitory NKG2A receptors, and exhibited elevated CXCR3 expression. CD16, NKG2A, and NKp46 expression were shown to be increased in stage IIIA breast cancer patients. TD-LNs contained a large proportion of activated CD56CD16 NK cells with high expression of NKG2A. We also showed that a subset of LN NK cells expressed PD-1, expression of which was correlated with NKp30 and NKG2C expression. LN NK cell activation status was evaluated by degranulation potential and lytic capacity toward breast cancer cells. NK cells from TD-LNs degranulated after coculture with breast cancer cell lines. Cytokine-activated TD-LN NK cells exerted greater lysis of breast cancer cell lines than HD-LN NK cells and preferentially lysed the HLA class I MCF-7 breast cancer cell line. TD-LNs from breast cancer patients, thus, contained activated lytic NK cells. The expression of inhibitory receptor NKG2A and checkpoint PD-1 by NK cells infiltrating breast cancer-draining LNs supports their potential as targets for immunotherapies using anti-NKG2A and/or anti-PD-1.

Pascale André, Caroline Denis, Caroline Soulas, Clarisse Bourbon-Caillet, Julie Lopez, Thomas

Arnoux, Mathieu Bléry, Cécile Bonnafous, Laurent Gauthier, Ariane Morel, Benjamin Rossi, Romain Remark, Violette Breso, Elodie Bonnet, Guillaume Habif, Sophie Guia, Ana Ines Lalanne, Caroline Hoffmann, Olivier Lantz, Jérôme Fayette, Agnès Boyer-Chammard, Robert Zerbib, Pierre Dodion, Hormas Ghadially, Maria Jure-Kunkel, Yannis Morel, Ronald Herbst, Emilie Narni-Mancinelli, Roger B Cohen, Eric Vivier (2018 Dec 4)

Anti-NKG2A mAb Is a Checkpoint Inhibitor that Promotes Anti-tumor Immunity by Unleashing Both T and NK Cells.

Cell : 1731-1743.e13 : DOI : S0092-8674(18)31322-9

Résumé

Checkpoint inhibitors have revolutionized cancer treatment. However, only a minority of patients respond to these immunotherapies. Here, we report that blocking the inhibitory NKG2A receptor enhances tumor immunity by promoting both natural killer (NK) and CD8 T cell effector functions in mice and humans. Monalizumab, a humanized anti-NKG2A antibody, enhanced NK cell activity against various tumor cells and rescued CD8 T cell function in combination with PD-x axis blockade. Monalizumab also stimulated NK cell activity against antibody-coated target cells. Interim results of a phase II trial of monalizumab plus cetuximab in previously treated squamous cell carcinoma of the head and neck showed a 31% objective response rate. Most common adverse events were fatigue (17%), pyrexia (13%), and headache (10%). NKG2A targeting with monalizumab is thus a novel checkpoint inhibitory mechanism promoting anti-tumor immunity by enhancing the activity of both T and NK cells, which may complement first-generation immunotherapies against cancer.

Grégory Beaune, Carles Blanch-Mercader, Stéphane Douezan, Julien Dumond, David Gonzalez-Rodriguez, Damien Cuvelier, Thierry Ondarçuhu, Pierre Sens, Sylvie Dufour, Michael P Murrell, Françoise Brochard-Wyart (2018 Dec 4)

Spontaneous migration of cellular aggregates from giant keratocytes to running spheroids.

Proceedings of the National Academy of Sciences of the United States of America : 12926-12931 : DOI : 10.1073/pnas.1811348115

Résumé

Despite extensive knowledge on the mechanisms that drive single-cell migration, those governing the migration of cell clusters, as occurring during embryonic development and cancer metastasis, remain poorly understood. Here, we investigate the collective migration of cell on adhesive gels with variable rigidity, using 3D cellular aggregates as a model system. After initial adhesion to the substrate, aggregates spread by expanding outward a cell monolayer, whose dynamics is optimal in a narrow range of rigidities. Fast expansion gives rise to the accumulation of mechanical tension that leads to the rupture of cell-cell contacts and the nucleation of holes within the monolayer, which becomes unstable and undergoes dewetting like a liquid film. This leads to a symmetry breaking and causes the

entire aggregate to move as a single entity. Varying the substrate rigidity modulates the extent of dewetting and induces different modes of aggregate motion: « giant keratocytes, » where the lamellipodium is a cell monolayer that expands at the front and retracts at the back; « penguins, » characterized by bipedal locomotion; and « running spheroids, » for nonspreading aggregates. We characterize these diverse modes of collective migration by quantifying the flows and forces that drive them, and we unveil the fundamental physical principles that govern these behaviors, which underscore the biological predisposition of living material to migrate, independent of length scale.

Partouche D., Turbant F., El Hamoui O., Campidelli C., Bombled M., Trépout S., Wien F., Arluison V. (2018 Dec 1)

Epigallocatechin Gallate Remodelling of Hfq Amyloid-Like Region Affects *Escherichia coli* Survival

Pathogens : 7 : 95 : DOI : 10.3390/pathogens7040095

Résumé

Hfq is a pleiotropic regulator that has key roles in the control of genetic expression. The protein noticeably regulates translation efficiency and RNA decay in Gram-negative bacteria, due to the Hfq-mediated interaction between small regulatory noncoding RNA and mRNA. This property is of primary importance for bacterial adaptation and virulence. We have previously shown that the Hfq E. coli protein, and more precisely its C-terminal region (CTR), self-assembles into an amyloid-like structure. In the present work, we demonstrate that epigallocatechin gallate (EGCG), a major green tea polyphenol compound, targets the Hfq amyloid region and can be used as a potential antibacterial agent. We analysed the effect of this compound on Hfq amyloid fibril stability and show that EGCG both disrupts Hfq-CTR fibrils and inhibits their formation. We show that, even if EGCG affects other bacterial amyloids, it also specifically targets Hfq-CTR in vivo. Our results provide an alternative approach for the utilisation of EGCG that may be used synergistically with conventional antibiotics to block bacterial adaptation and treat infections.

Prado Martins R., Findakly S., Daskalogianni C., Teulade-Fichou M.P., Blondel M., Fåhraeus R. (2018 Nov 29)

In Cellulo Protein-mRNA Interaction Assay to Determine the Action of G-Quadruplex-Binding Molecules

Molecules : 23 : 3124 : DOI : 10.3390/molecules23123124

Résumé

Protein-RNA interactions (PRIs) control pivotal steps in RNA biogenesis, regulate multiple physiological and pathological cellular networks, and are emerging as important drug targets. However, targeting of specific protein-RNA interactions for therapeutic developments is still poorly advanced. Studies and manipulation of these interactions are technically challenging and in vitro drug screening assays are often hampered due to the

complexity of RNA structures. The binding of nucleolin (NCL) to a G-quadruplex (G4) structure in the messenger RNA (mRNA) of the Epstein-Barr virus (EBV)-encoded EBNA1 has emerged as an interesting therapeutic target to interfere with immune evasion of EBV-associated cancers. Using the NCL-EBNA1 mRNA interaction as a model, we describe a quantitative proximity ligation assay (PLA)-based in cellulo approach to determine the structure activity relationship of small chemical G4 ligands. Our results show how different G4 ligands have different effects on NCL binding to G4 of the EBNA1 mRNA and highlight the importance of in-cellulo screening assays for targeting RNA structure-dependent interactions.

Daniel A Fletcher, Junsang Doh, Matthieu Piel (2018 Nov 27)
Preface.
Methods in cell biology : xiii : DOI : S0091-679X(18)30175-4

Résumé

Clotilde Théry, Kenneth W Witwer, Elena Aikawa, Maria Jose Alcaraz, Gregory Lavieu, ... Lorena Martin-Jaular, ... Mathilde Mathieu, ... Mercedes Tkach,... , Ewa K Zuba-Surma (2018 Nov 23)
Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines.
Journal of extracellular vesicles : 1535750 : DOI : 10.1080/20013078.2018.1535750

Résumé

The last decade has seen a sharp increase in the number of scientific publications describing physiological and pathological functions of extracellular vesicles (EVs), a collective term covering various subtypes of cell-released, membranous structures, called exosomes, microvesicles, microparticles, ectosomes, oncosomes, apoptotic bodies, and many other names. However, specific issues arise when working with these entities, whose size and amount often make them difficult to obtain as relatively pure preparations, and to characterize properly. The International Society for Extracellular Vesicles (ISEV) proposed Minimal Information for Studies of Extracellular Vesicles (« MISEV ») guidelines for the field in 2014. We now update these « MISEV2014 » guidelines based on evolution of the collective knowledge in the last four years. An important point to consider is that ascribing a specific function to EVs in general, or to subtypes of EVs, requires reporting of specific information beyond mere description of function in a crude, potentially contaminated, and heterogeneous preparation. For example, claims that exosomes are endowed with exquisite and specific activities remain difficult to support experimentally, given our still limited knowledge of their specific molecular machineries of biogenesis and release, as compared with other biophysically similar EVs. The MISEV2018 guidelines include tables and outlines of suggested protocols and steps to follow to document specific EV-associated functional activities. Finally, a checklist is provided with summaries of key points.

Verga D., Nguyen C.H., Dakir M., Coll J.L., Teulade-Fichou M.P., Molla A. (2018 Nov 20)
Polyheteroaryl Oxazole/Pyridine-based compounds selected in vitro as G-quadruplex ligands inhibit Rock kinase and exhibit antiproliferative activity
Journal of Medicinal Chemistry : 61 : 10502-10518 : DOI : 10.1021/acs.jmedchem.8b01023

Résumé

Heptaheteroaryl compounds comprised of oxazole and pyridine units (TOxaPy) are quadruplex DNA (G4)-interactive compounds. Herein, we report on the synthesis of parent compounds bearing either amino side chains (TOxaPy-1-5) or featuring an isomeric oxazole-pyridine central connectivity (iso-TOxapy, iso-TOxapy 1-3) or a bipyridine core (iso-TOxabiPy). The new isomeric series showed significant G4-binding activity in vitro and remarkably 3 compounds (iso-TOxaPy, iso-TOxaPy-1, iso-TOxabiPy) exhibited high antiproliferative activity towards a tumor panel of cancer cell lines. However, these compounds do not behave as typical G-quadruplex binders and the kinase profiling assay revealed that the best antiproliferative molecule iso-TOxaPy selectively inhibited Rock-2. The targeting of Rock kinase was confirmed in cells by the dephosphorylation of Rock-2 substrates, the decrease of stress fibers and peripheral focal adhesions, as well as the induction of long neurite-like extensions. Remarkably two of these molecules were able to inhibit the growth of cells organized as spheroids.

Maheva Andriatsilavo, Marine Stefanutti, Katarzyna Siudeja, Carolina N Perdigoto, Benjamin Boumard, Louis Gervais, Alexandre Gillet-Markowska, Lara Al Zouabi, François Schweisguth, Allison J Bardin (2018 Nov 20)
Spen limits intestinal stem cell self-renewal.
PLoS genetics : e1007773 : DOI : 10.1371/journal.pgen.1007773

Résumé

Precise regulation of stem cell self-renewal and differentiation properties is essential for tissue homeostasis. Using the adult Drosophila intestine to study molecular mechanisms controlling stem cell properties, we identify the gene split-ends (spen) in a genetic screen as a novel regulator of intestinal stem cell fate (ISC). Spen family genes encode conserved RNA recognition motif-containing proteins that are reported to have roles in RNA splicing and transcriptional regulation. We demonstrate that spen acts at multiple points in the ISC lineage with an ISC-intrinsic function in controlling early commitment events of the stem cells and functions in terminally differentiated cells to further limit the proliferation of ISCs. Using two-color cell sorting of stem cells and their daughters, we characterize spen-dependent changes in RNA abundance and exon usage and find potential key regulators downstream of spen. Our work identifies spen as an important regulator of adult stem cells in the Drosophila intestine, provides new insight to Spen-family protein functions, and may also shed light on Spen's mode of action in other developmental contexts.